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stage thereof to the two or more mRNA species or two or more cDNA species transcribed from said RNA species, wherein said mRNA species or cDNA species are immobilized on a solid support; and

- Es (e) assessing the amount of hybridization, so as to determine the degree of correlation indicative of the presence of said disease or stage thereof, and so as to diagnose or identify said disease or a stage thereof in said test human.

Claim 93. The method as claimed in Claim 90, 91 or 92, wherein said cells are isolated from tissue, body fluid or body waste of said eukaryotic organism.

Claim 94. The method as claimed in Claim 93, wherein said body fluid is blood. --

REMARKS

Claims 37, 56, 57 and 58 have been amended, *inter alia*, to include the recitation of cancelled Claim 44 therein.

The amended claims refer to cells which have not contacted the area of said disease. Support this amendment can be found, *inter alia*, in Examples 1, 2 and 6 of the present specification, and at page 23, lines 15-19 of the present specification, wherein it is taught that the effects of gene expression are not isolated to the areas of apparent disease due to the effect of the disease on all parts of the body.

More specifically, Example 1 describes a method in which Alzheimer's disease is diagnosed by taking a blood sample. The blood:brain barrier, whilst allowing the transmission of small

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molecules, does not allow the passage of cells. Thus, in this example, the cells examined in the blood are not obtained from the area of the disease (i.e., are not obtained from the brain), rather the cells are obtained from a part of the organism distant to the area of disease. Further, the cells examined have not contacted the brain cells (the area of disease) since the brain cells are not able to pass through the blood:brain barrier into the circulation. Similarly, circulating lymphocytes in the blood are not able to pass through the blood:brain barrier to have contact with the brain cells. Thus, Example 1 teaches that cells (in this case circulating lymphocytes) which have not contacted the area of disease (in this case the brain) are examined.

Example 2 discloses a method of diagnosing a further disease of the brain (senile dementia) by examining a blood sample as described in Example 1. Thus, Example 2 teaches that cells (in this case circulating lymphocytes) which have not contacted the area of disease (in this case the brain) are examined.

In Example 6, the roots of Norwegian spruce are infected with the fungal pathogen *Pythium dimorphum*. This results in an infection which is localized to only the roots of the plant. That is, no infection of the needles occurs. In this example, the needles were collected and the transcript patterns of cells isolated from the needles were examined. Clearly, the cells of the needles are obtained from a part of the organism distant to the area of the disease. Further, unlike, for example, mammals, plants do not have a circulation system which circulates cells.

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Thus, cells obtained from needles are not cells which have contacted the area of disease, i.e., the roots. The difference in expression observed in the needles of infected plants relative to control plants (see Figure 2, day 4 control versus *Pythium dimorphum* needles) clearly reflects a systemic effect in which cells which have not contacted the area of disease (i.e., needles cells which have not contacted root cells) are examined.

New Claims 78-94, directed to Alzheimer's disease, refer to cells being obtained from a part of the human distant to the area of the disease. These claims are supported at page 23 of the present application, and in particular Example 1. Again, in Example 1, the cells which are used are obtained from a part of the organism (e.g., the peripheral blood system) which is distant to the area of the disease (the brain).

Turning now to the outstanding Office Action.

In paragraph 2, on page 2 of the Office Action, the Examiner indicates that she has not considered Lonneborg et al, Fujioka, Schena, Shalon et al since these references were not included with the Information Disclosure Statement. Further, the Examiner states Zhi-Xin et al was not properly cited since no journal reference was listed.

Accordingly, Applicants submit herewith additional copies of the alleged missing references. The Examiner is requested to provide a Form 1449 indicating consideration of the cited references.

As to the Zhi-Xin et al, it appears that the Examiner has considered and fully cited this reference in the Office Action. Further, it is Applicants' understanding that the Examiner has

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obtained and considered a complete English language translation of this reference. Thus, it is Applicants understanding that no further action needs to be taken regarding the same.

In paragraph 4, on page 3 of the Office Action, the Examiner objects to Claims 60-65 under 37 C.F.R. § 1.75(c) as being in improper multiple dependent form.

Claims 60-62 and 64-65 are dependent upon Claims 57, 58 or 59. Claims 57, 58 or 59 are singly dependent claims. That is, Claim 57 is dependent upon Claim 53, Claim 58 is dependent upon Claim 53 and Claim 59 is dependent upon Claim 53. Thus, Applicants respectfully submit that the Examiner's rejection is improper.

Nonetheless, in order to overcome this objection, Applicants have amended Claims 60-62 and 64-65, provided new Claims 66-68, 70-74 and 76-77, which correspond to Claims 60-62 and 64-65, but which are dependent individually on Claims 58 or 59; as well as provide new Claims 69 and 75, which correspond to Claim 63, but depend on the respective new claims.

In paragraph 6, on page 3 of the Office Action, the Examiner rejects Claims 37-65 under 35 U.S.C. § 112, first paragraph as containing new matter.

Specifically, the Examiner states that the recitation "and originate from" presents new matter.

While Applicants submit that this expression is fully supported, *inter alia*, by Examples 1-2 and 6 of the present application, solely in order to advance prosecution, the claims have been amended to delete the expression "and originate from".

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Thus, Applicants respectfully submit that the Examiner's rejection has been rendered moot.

In paragraph 7, on page 4 of the Office Action, the Examiner rejects Claims 37-65 under 35 U.S.C. § 112, first paragraph.

Specifically, the Examiner states that while the specification is enabling for methods for obtaining isolated selected mRNA species useful for diagnosing or identifying a disease or condition, wherein the mRNA is isolated from cells that are obtained from a part of an organism distant to the area of disease, such does not provide enablement for a method for obtaining isolated selected mRNA species for diagnosing or identifying a disease or condition wherein the mRNA is isolated from cells that are obtained from and originate from a part of an organism distant to the area of disease.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Initially, the Examiner is requested to note that Applicants hereby cancel Claims 53-55, thus only Claims 37-52 and 56-65 remain subject to this rejection.

Again, as discussed above, Applicants respectfully submit that, *inter alia*, Examples 1-2 and 6 fully support a method for obtaining isolated selected mRNA species for diagnosing or identifying a disease or condition wherein the mRNA species are isolated from cells that are obtained from and originate from a part of an organism distant to the area of disease.

More specifically, the Examiner is requested to note that Example 6, which is not speculative, shows that systemic effects

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are observed in cells which do not originate from, and have not contacted the area of disease. Figure 2 shows that needles from a control plant exhibit different transcript levels compared to needles derived from a root-infected plant. Example 6 thus, illustrates that the expression of various genes are affected distant to the area of disease, which leads to a pattern or fingerprint of expression which can be used diagnostically to determine if a test sample is derived from a normal or diseased plant. Hence, the specification teaches isolating samples distant to the area of disease and using cells which do not originate from the area of disease, wherein the cells have not contacted the area of disease, and that the gene expression levels of these cells (and corresponding normal cells) can be used diagnostically to determine the state of the plant from which the cells were derived.

The above experiments (Examples 1-2 and 6) represent 3 diverse examples which illustrate the general utility of the present invention. In order to satisfy an enablement requirement it is necessary to address whether the skilled person is taught how to make and use the invention. The specification clearly teaches which samples to use, as described above. Once the skilled person is directed to the appropriate sample, the skilled person can examine the gene transcript patterns in the cells of that sample from normal compared to diseased samples and so identify transcripts whose level of expression are informative, i.e., reflect differences in expression in the different samples which can be used diagnostically.

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The Examiner is requested to note that Applicants will shortly file a Declaration under Rule 132 further demonstrating the operability of the claimed method with respect to the various diseases based on the teachings in the specification.

The Examples described in the present specification and the results in the Declaration demonstrate that systemic influence of the disease on the entire body is a general principle that occurs in diverse species with diverse diseases, and thus allow a reasonable prediction that this effect will be observed in all species and all diseases. It is believed that this systemic effect results from the release of various signals in the body when the body is diseased, and that the particular cocktail of signals, and hence their effects on gene transcription, are specific to a particular disease.

In any event, as noted above, in view of the amendments to the claims to delete the expression "and originate from", the Examiner's rejection has been rendered moot.

In paragraph 8, on page 8 of the Office Action, the Examiner rejects Claims 53-55 and 59-65 under 35 U.S.C. § 112, first paragraph.

Specifically, the Examiner states that the claims are drawn to a gene transcript pattern probe kit and method for using the kit and diagnosis of disease, and depend from base claims which describe a method for isolating the probes in question.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Initially, the Examiner is requested to note that Applicants hereby cancel kit Claims 53-55.

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Furthermore, Claim 59 (and also Claims 57 and 58) which referred to the kits of preceding claims have been amended such that they no longer refer to the kit claims. That is, Claim 57 has been amended to refer to immobilized mRNA or cDNA species which have been isolated from samples which have not contacted the area of said disease and are obtained from a part of the organism distant to the area of disease, and which show different levels of expression in normal versus disease cells.

Accordingly, Applicants respectfully submit that the claims meet the written description requirement, and thus request withdrawal of the Examiner's rejection.

In paragraph 10, on page 9 of the Office Action, the Examiner rejects Claims 37, 40-42, 45-46 and 48-51 under 35 U.S.C. 102(e) as being anticipated by Ralph et al.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Claim 44 has not been included in this rejection, and thus been held to be novel over Ralph et al. Hence, in view of the amendment to Claim 37 to include the recitation of Claim 44 therein, the Examiner's rejection has been rendered moot.

In any event, the Examiner is requested to note that Ralph et al (like Zhi-Xin et al, discussed in detail below) fails to teach or suggest that cells that have not contacted the area of disease are informative and can be used for diagnostic purposes.

More specifically, the basis of the invention of Ralph et al is set out in column 5, line 1 et seq thereof as relying "upon detecting a response of circulating leukocytes to

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the disease site". Thus, Ralph et al is concerned with examining diseases which produce a secondary response, namely an immune response (see column 5, lines 15-34 thereof).

Ralph et al identifies samples that may be used for analysis therein as "any sample that is suspected of containing a disease state-specific antigen, such as a lymph node, tissue section...or any other biological fluid that comes into contact with the diseased tissues".

The immune response activation which is described in the above passages is demonstrated by the type of genes which are identified by Ralph et al as showing altered expression in normal versus diseased patients. Ralph et al refers to "molecular changes in host immune response genes that occur during the process of malignancy" (column 95, lines 21-22 thereof), and when examining patients with metastatic cancer observed changes in immune function related genes, IL-8 and IL-10.

On the other hand, in the present invention, for the first time, it was recognized that no contact with the area of disease is required, and that cells that have simply been affected in other parts of the body by systemic effects, represent an important and informative group of cells. The recognition of these cells as providing a diagnostic tool of wide application is clearly unobvious over the prior art, which is silent about the merits of such cells and certainly does not teach or suggest their use in any diagnostic methods.

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Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Ralph et al, and thus request withdrawal of the Examiner's rejection.

In paragraph 11, on page 10 of the Office Action, the Examiner rejects Claims 37-51 under 35 U.S.C. § 103 as being unpatentable over Wadhwa et al in view of Zhi-Xin et al.

Specifically, the Examiner states that while Wadhwa et al does not teach that the cells are obtained from and originate from a part of the organism distant from the area of disease, Zhi-Xin et al teaches IL2R mRNA expression in peripheral blood mononuclear cells of patients with lung cancer compared to a control group, and that the IL-2R expression level was closely related to prognosis in cancer patients. Thus, the Examiner contends that Zhi-Xin et al provides an example of differential expression that is diagnostic of cancer in cells that are obtained from and originate from a site distant from the tumor.

Hence, the Examiner concludes that it would have been obvious to sample cells which are obtained from and originate distant from the site of disease, such as blood cells, as taught by Zhi-Xin et al in the method of Wadhwa et al in order to identify additional mRNA species for disease detection, as claimed in the present application.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Wadhwa et al teaches the identification of differentially expressed genes in a transformed cell line versus a normal cell line.

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Wadhwa et al does not teach or suggest examination of cells from a eukaryotic organism as claimed in the present invention, and thus clearly does not teach or suggest examination of cells obtained distant to the area of disease, as claimed in the present invention.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Wadhwa et al, and for the following reasons, it is clear that Zhi-Xin et al does not provide the deficiencies which exists therein.

Zhi-Xin et al does not teach or suggest the examination of cells which have not contacted the area of said disease. Zhi-Xin et al discloses alterations in IL-2R and mRNA expression levels in PBMC from patients with or without metastatic lung cancer. As taught at page 9 of the English translation of Zhi-Xin et al prepared by the U.S. Patent and Trademark Office and provided to Applicants at the Examiner Interview on June 11, 2002, the molecule [IL-2R] under study therein is considered to be a marker of active T lymphocytes. Further, on page 10 thereof, the last 7 lines, it is taught that "lymphocytes of the patients in the group without metastasis were already sensitized by the cancer cells", and essentially the same comments are repeated later in the same paragraph. Thus, Zhi-Xin et al looks at lymphocytes which have been activated by contact with the cancer cells. This is reflected in the type of molecule whose expression is increased, namely a molecule related to immune function, i.e., IL-2R.

The Examiner is requested to note that in Table 1 of Zhi-Xin et al, the level of IL-2R mRNA in various samples is

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disclosed. In view of the very large standard deviations, no particular conclusion may be drawn regarding the level of expression in the various classes. Furthermore, it should be noted that from Table 2, the "Group without metastasis" includes patients with stage II and III disease, at which stage at least disseminated cells are expected in the peripheral bloodstream. Thus, in both the metastasis group and the non-metastasis group, disease cells are expected in the peripheral blood system which would allow the immune response reaction to occur. It should further be noted that Zhi-Xin et al merely provides an observation regarding IL-2R mRNA during the progression of lung cancer. There is no evidence therein that such a marker could be used diagnostically, and indeed there is no suggestion to do so. It is clear from Table 1 that, for example, a level of say 200 pg/ml IL-2R mRNA, could be attributed to a metastatic patient, a patient without metastasis or a healthy person, in view of the large variation of IL-2R mRNA levels observed in such patients. Thus, whilst the level of IL-2R mRNA may inform the skilled person about the activation state of the lymphocytes of a pre-diagnosed patient, it would certainly provide no useful information for diagnostic purposes.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Wadhwa et al alone or in view of Zhi-Xin et al, and thus request withdrawal of the Examiner's rejection.

In paragraph 12, on page 12 of the Office Action, the Examiner rejects Claims 37, 40-42, 45-46 and 48-51 under

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35 U.S.C. § 103 as being unpatentable over Graber et al in view of Zhi-Xin et al.

Specifically, the Examiner states that while Graber et al does not teach a method wherein the cells whose mRNA is isolated are obtained from and originate from part of the organism distant to the area of said disease, Zhi-Xin et al teaches such.

Hence, the Examiner concludes that it would have been obvious to sample cells which are obtained from and originate distant from the site of disease, such as blood cells, as taught by Zhi-Xin et al in the method of Graber et al in order to identify additional mRNA species for disease detection, as claimed in the present application.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Graber et al is similar to Wadhwa et al, insofar as it simply concerns methods of identifying transcripts which are differentially expressed, in this case in disease versus non-disease tissue. Thus, even when combined with the teachings of Zhi-Xin et al, the present invention would not be obtained since such a combination does not give rise to using cells which have not contacted the area of disease, as claimed in the present application.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Graber et al alone or in view of Zhi-Xin et al, and thus request withdrawal of the Examiner's rejection.

In paragraph 13, on page 14 of the Office Action the Examiner rejects Claims 53-58 under 35 U.S.C. § 103 as being

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unpatentable over Wadhwa et al in view of Zhi-Xin et al, and further in view of the Stratagene Catalog.

Specifically, the Examiner states that Wadhwa et al in view of Zhi-Xin et al do not teach the packaging of immobilized cDNA species into a kit, nor do they teach this method as a method for making a kit. However, the Examiner states that the Stratagene Catalog teaches gene characterization kits. Thus, the Examiner concludes that it would have been obvious to produce a kit containing the cDNA on a solid support, and other reagents useful for gene transcript comparisons as claimed in the present application.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Initially, the Examiner is requested to note that Applicants hereby cancel Claims 53-55.

Furthermore, Claims 56-58 have been amended to refer to probes isolated from cells which have not contacted the area of disease. Thus, as described above, the cited prior art does not teach or suggest the use of such cells.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Wadhwa et al alone or in view of Zhi-Xin et al and the Stratagene Catalog, and thus request withdrawal of the Examiner's rejection.

In paragraph 14, on page 15 of the Office Action, the Examiner rejects Claims 59-64 under 35 U.S.C. § 103 as being unpatentable over Wadhwa et al in view of Zhi-Xin et al and in view of the Stratagene Catalog, and further in view of Seilhamer et al.

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Specifically, the Examiner states that Wadhwa et al in view of Zhi-Xin et al and in view of the Stratagene Catalog do not teach a method in which a test sample is compared to a known sample for diagnosis of disease, but that such would have been obvious in view of Seilhamer et al.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Seilhamer et al fails to cure the above-discussed deficiencies in the prior art, i.e., Seilhamer et al does not direct the skilled person to examine cells which have not contacted the area of disease, as claimed in the present invention.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Wadhwa et al alone or in view of Zhi-Xin et al and Seilhamer et al, and thus request withdrawal of the Examiner's rejection.

In paragraph 15, on page 16 of the Office Action, the Examiner rejects Claims 53 and 54 under 35 U.S.C. § 103 as being unpatentable over Schena et al in view of the Stratagene Catalog.

In view of the cancellation of Claims 53 and 54, the Examiner's rejection has been rendered moot.

In view of the amendments to the claims and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

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The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,



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A P P E N D I X

Marked-Up Version of Changes

IN THE CLAIMS:

Claims 38, 44 and 53-55 are being cancelled.

The claims are amended as follows:

Claim 37. (Amended) A method of obtaining isolated selected mRNA species or isolated selected cDNA species useful for diagnosing or identifying a disease [or condition] or stage thereof in a eukaryotic organism comprising the steps of:

- (a) isolating mRNA from cells of one or more eukaryotic organisms which are known to have said disease [or condition] or a stage thereof (diseased sample), wherein said cells have not contacted the area of said disease and are obtained from[, and originate from,] a part of said organism distant to the area of said disease, wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA;
- (b) isolating mRNA from corresponding cells of one or more corresponding normal eukaryotic organisms (normal sample), wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA;
- (c) separating, by a non-sequence based separation technique, mRNA species or cDNA species present within each of the resulting isolated mRNA or isolated cDNA of step (a) and step (b), wherein the resulting separated mRNA species are

optionally subject to reverse transcription to obtain separated cDNA species;

- (d) selecting between 10 and 500 [two or more] mRNA species or between 10 and 500 [two or more] cDNA species from the resulting separated mRNA species or resulting separated cDNA species obtained in step (c), respectively, which are present at a different level in the normal sample than in the diseased sample by identifying a signal corresponding to each mRNA species or cDNA species, wherein the resulting selected between 10 and 500 [two or more] mRNA species are optionally subjected to reverse transcription to obtain between 10 and 500 [two or more] selected cDNA species; and
- (e) isolating the resulting between 10 and 500 [two or more] selected mRNA species or resulting between 10 and 500 [two or more] selected cDNA species obtained in step (d) to obtain isolated selected mRNA species or isolated selected cDNA species, wherein the resulting isolated selected mRNA species are optionally subjected to reverse transcription to obtain isolated selected cDNA species.

Claim 39. (Amended) The method as claimed in Claim [38] 56, wherein, prior to immobilizing in step (f), the resulting isolated selected mRNA species or isolated selected cDNA species of step (e) are amplified.

Claim 47. (Amended) The method as claimed in Claim [38] 56, wherein said solid support is a filter.

Claim 56. (Amended) A method of preparing a gene transcript pattern probe kit comprising the steps of:

- (a) isolating mRNA from cells of one or more eukaryotic organisms which are known to have [said] a disease [or condition] or a stage thereof (diseased sample), wherein said cells have not contacted the area of said disease and are obtained from[, and originate from,] a part of said organism distant to the area of said disease, wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA;
- (b) isolating mRNA from corresponding cells of one or more corresponding normal eukaryotic organisms (normal sample), wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA;
- (c) separating, by a non-sequence based separation technique, mRNA species or cDNA species present within each of the resulting isolated mRNA or isolated cDNA of step (a) and step (b), wherein the resulting separated mRNA species are optionally subject to reverse transcription to obtain separated cDNA species;
- (d) selecting between 10 and 500 [two or more] mRNA species or between 10 and 500 [two or more] cDNA species from the resulting separated mRNA species or resulting separated cDNA species obtained in step (c), respectively, which are present at a different level in the normal sample than in the

diseased sample by identifying a signal corresponding to each mRNA species or cDNA species, wherein the resulting selected between 10 and 500 [two or more] mRNA species are optionally subjected to reverse transcription to obtain between 10 and 500 [two or more] selected cDNA species;

- (e) isolating the resulting between 10 and 500 [two or more] selected mRNA species or resulting between 10 and 500 [two or more] selected cDNA species obtained in step (d) to obtain isolated selected mRNA species or isolated selected cDNA species, wherein the resulting isolated selected mRNA species are optionally subjected to reverse transcription to obtain isolated selected cDNA species; and
- (f) immobilizing the resulting isolated selected mRNA species or isolated selected cDNA species of step (e) on at least one solid support so as to form a gene transcript pattern probe kit.

Claim 57. (Amended) A method of preparing a standard gene transcript pattern characteristic of a disease [or condition] or stage thereof of a eukaryotic organism comprising the steps of:

- (a) isolating mRNA from cells of one or more eukaryotic organisms known to have said disease [or condition] or a stage thereof, (diseased sample) wherein said cells have not contacted the area of said disease and are obtained from[, and originate from,] a part of said organism distant to the area of said disease, wherein the

resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA; [and]

- (b) hybridizing the resulting isolated mRNA or isolated cDNA of step (a) to between 10 and 500 mRNA species which are present at a different level in cells in a normal sample than corresponding cells in a diseased sample, wherein the between 10 and 500 mRNA species or cDNA species are specific for said disease or stage thereof and wherein said cells have not contacted the area of said disease and are obtained from a part of said organism distant to the area of said disease, or to between 10 and 500 cDNA species transcribed from said mRNA species, wherein said mRNA or [the isolated selected mRNA species or isolated selected] cDNA species [which] are immobilized on a solid support [in the gene transcript pattern probe kit of Claim 53,]; and
- (c) assessing the amount of hybridisation so as to obtain said standard gene transcript pattern[, wherein the isolated selected mRNA species or isolated selected cDNA species are specific for said disease or condition or stage thereof].

Claim 58. (Amended) A method of preparing a test gene transcript pattern for a disease [or condition] or stage thereof comprising the steps of:

- (a) isolating mRNA from cells of a test eukaryotic organism, wherein said cells have not contacted the area of said disease and are obtained from[,

and originate from,] a part of said organism distant to the area of said disease, wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA; [and]

- (b) hybridizing the resulting isolated mRNA or isolated cDNA of step (a) to between 10 and 500 mRNA species which are present at a different level in cells in a normal sample than corresponding cells in a diseased sample, wherein the between 10 and 500 mRNA species or cDNA species are specific for said disease or stage thereof and wherein said cells have not contacted the area of said disease and are obtained from a part of said organism distant to the area of said disease, or to between 10 and 500 cDNA species transcribed from said mRNA species, wherein said mRNA or [the isolated selected mRNA species or isolated selected] cDNA species [which] are immobilized on a solid support [in the gene transcript pattern probe kit of Claim 53], and assessing the amount of hybridization so as to obtain said test gene transcript pattern[, wherein the isolated selected mRNA species or isolated selected cDNA species are specific for a said disease or condition or stage thereof].

Claim 59. (Amended) A method of diagnosing or identifying a disease [or condition] or stage thereof in a test eukaryotic organism comprising the steps of:

- (a) isolating mRNA from cells of a test eukaryotic organism, wherein said cells have not contacted the area of said disease and are obtained from[, and originate from,] a part of said organism distant to the area of said disease, wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA;
- (b) hybridizing the resulting isolated mRNA or isolated cDNA of step (a) to between 10 and 500 mRNA species which are present at a different level in cells in a normal sample than corresponding cells in a diseased sample, wherein the between 10 and 500 mRNA species or cDNA species are specific for said disease or stage thereof and wherein said cells have not contacted the area of said disease and are obtained from a part of said organism distant to the area of said disease, or to between 10 and 500 cDNA species transcribed from said mRNA species, wherein said mRNA or [the isolated selected mRNA species or isolated selected] cDNA species [which] are immobilized on a solid support [in the gene transcript pattern probe kit of Claim 53, and];
- (c) assessing the amount of hybridization so as to obtain a hybridization pattern[, wherein the isolated selected mRNA species or isolated selected cDNA species are specific for said disease or condition or stage thereof]; [and]
- [(c)] (d) comparing the resulting hybridization pattern obtained in step [(b)] (c) with a hybridization

pattern obtained by hybridizing isolated mRNA or isolated cDNA prepared from corresponding cells from one or more corresponding eukaryotic organisms known to have said disease [or condition] or stage thereof to the between 10 and 500 [isolated selected] mRNA species or between 10 and 500 [isolated selected] cDNA species transcribed from said mRNA species, wherein said mRNA species or cDNA species [which] are immobilized [in said gene transcript pattern probe kit] on a solid support; and

- (e) assessing the amount of hybridization, so as to determine the degree of correlation indicative of the presence of said disease [or condition] or stage thereof, and so as to diagnose or identify said disease [or condition] or a stage thereof in said test eukaryotic organism.

Claim 60. (Amended) The method as claimed in Claim 57[, 58 or 59], wherein said organism is human.

Claim 61. (Amended) The method as claimed in Claim 57[, 58 or 59], wherein said disease is cancer.

Claim 62. (Amended) The method as claimed in Claim 57[, 58 or 59], wherein said cells are isolated from tissue, body fluid or body waste of said eukaryotic organism.

Claim 64. (Amended) The method as claimed in Claim 57[, 58 or 59], wherein said disease is selected from the group comprising stomach, lung, breast, prostate gland, bowel and skin cancer.

Claim 65. (Amended) The method as claimed in Claim 57[, 58 or 59], wherein said disease is Alzheimer's disease.

New Claims 66-94 are being added.